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Research report

ATP-sensitive potassium-channel inhibitor glibenclamide attenuates HPA axis hyperactivity, depression- and anxiety-related symptoms in a rat model of Alzheimer's disease

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ABSTRACT

Affective disorders including depression and anxiety are among the most prevalent behavioral abnormalities in patients with Alzheimer's disease (AD), which affect the quality of life and progression of the disease. Dysregulation of the hypothalamic-pituitary-adrenal-(HPA) axis has been reported in affective disorders and AD. Recent studies revealed that current antidepressant drugs are not completely effective for treating anxiety- and depression-related disorders in people with dementia. ATP-sensitive-potassium-(K_{ATP}) channels are well-known to be involved in AD pathophysiology, HPA axis function and the pathogenesis of depression and anxiety-related behaviors. Thus, targeting of K_{ATP} channel may be a potential therapeutic strategy in AD. Hence, we investigated the effects of intracerebroventricular injection of Aβ25-35 alone or in combination with glibenclamide, K_{ATP} channel inhibitor on depression- and anxiety-related behaviors as well as HPA axis response to stress in rats. To do this, non-Aβ25-35- and Aβ25-35-treated rats were orally treated with glibenclamide, then the behavioral consequences were assessed using sucrose preference, forced swim, light-dark box and plus maze tests. Stress-induced corticosterone levels following forced swim and plus maze tests were also evaluated as indicative of abnormal HPA-axis-function. Aβ25-35 induced HPA axis hyperreactivity and increased depression- and anxiety-related symptoms in rats. Our results showed that blockade of K_{ATP} channels with glibenclamide decreased depression- and anxiety-related behaviors by normalizing HPA axis activity in Aβ25-35-treated rats. This study provides additional evidence that Aβ administration can induce depression- and anxiety-like symptoms in rodents, and suggests that K_{ATP} channel inhibitors may be a plausible therapeutic strategy for treating affective disorders in AD patients.

1. Introduction

Alzheimer disease (AD) is one of the most common neurodegenerative diseases affecting millions of individuals in developing societies, but the exact pathological cause remained unknown (Kalaria et al., 2008; Wood and Cummings, 2004). To date, the amyloid hypothesis has been considered as the most prevalent theory to explain the pathophysiology of AD. According to this hypothesis, one of the neuropathology characteristics of AD is an accumulation of senile and neurofibrillary tangles, mainly composed of β-amyloid (Aβ) peptide and highly phosphorylated tau proteins in the brain (Accardi et al., 2012; Hardy and Selkoe, 2002; Karran et al., 2011). These structures accumulate progressively in different brain regions, leading to memory impairment and neuronal damage (Babri et al., 2014; Fjell et al., 2014).

In the last decade, chronic stress and adverse lifestyle have been shown to be serious risk factors for development and progression of AD in humans (Marcello et al., 2015; Pardon, 2011; Zvěřová et al., 2013). Stress was found to contribute significantly in accelerating AD-related phenotypes and cognitive decline (Sotiropoulos et al., 2011). In addition, experimental stressful conditions were shown to aggravate Aβ-pathology in animal models of AD (Baglietto-Vargas et al., 2015; Green et al., 2006; Jeong et al., 2006). The most important stress system which is physiologically activated in response to actual or presumed environmental challenges is hypothalamic pituitary adrenal (HPA) axis (Noschang et al., 2012). Activation of this neuroendocrine stress system triggers the release of glucocorticoid hormones including cortisol in humans and corticosterone in rodents from the adrenal cortex (Brureau et al., 2013). These steroid hormones can easily cross blood-brain

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